Department of Health and Human Services

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE OF MENTAL HEALTH

National Advisory Mental Health Council

Minutes of the 203rd Meeting

May 9, 2003

Minutes of the 203rd Meeting of the National Advisory Mental Health Council

The National Advisory Mental Health Council (NAMHC) convened its 203rd meeting in closed session for the purpose of reviewing grant applications at 10:30 a.m. on May 8, 2003, in the Neuroscience Center, Rockville, Maryland, and adjourned at approximately 5:30 p.m. (see Appendix A: Review of Applications). The NAMHC reconvened in open session at 8:30 a.m. on May 9, 2003, in Building 31C, Conference Room 10, on the main campus of the National Institutes of Health (NIH), Bethesda, Maryland. In accordance with Public Law 92-463, this policy meeting was open to the public until its adjournment at 1:40 p.m. Thomas R. Insel, M.D., Director, National Institute of Mental Health (NIMH), chaired the meeting.

Council Members Present at Closed and/or Open Sessions (see Appendix B for Council Roster):
Robert O. Boorstin
Javier I. Escobar, M.D.
Susan M. Essock, Ph.D.
Susan Folkman, Ph.D.
Megan R.Gunnar, Ph.D.
Renata J. Henry
Norwood W. Knight-Richardson, M.D.
Henry A. Lester, Ph.D.
Jeffrey A. Lieberman, M.D.
James L. McClelland, Ph.D.
James P. McNulty
Eric J. Nestler, M.D., Ph.D.
Charles F. Reynolds, III, M.D.
Ming T. Tsuang, M.D., Ph.D.
Karen Dineen Wagner, M.D., Ph.D.

Chairperson
Thomas R. Insel, M.D.

Executive Secretary
Jane A. Steinberg, Ph.D.

Council Members Absent
Elaine Sanders-Bush, Ph.D.
Larry R. Squire, Ph.D.

Ex-Officio Council Members Present
Elspeth Cameron Ritchie, M.D., Department of Defense
Robert Freedman, M.D., Colorado Veterans Administration Hospital

Liaison Representative, Substance Abuse and Mental Health Services Administration, Present
Gail Hutchings, M.P.A., Acting Director, Center for Mental Health Services

Members of the Public Present for Portions of the Open Policy Session
Michelle Alonso, Anxiety Disorders Association of America
Heather Biggar Kersey, Society for Research in Child Development
Thomas J. Coates, University of California San Francisco
Judith Cornelius, Child and Adolescent Bipolar Foundation
Stuart Cox, Child and Adolescent Bipolar Foundation
Jill Egeth, Federation of Behavioral, Psychological and Cognitive Services
Cynthia Folcarelli, National Mental Health Association

E. Aracelis Francis, Council on Social Work Education
Marilyn Goldstein, National Education Alliance for Borderline Personality Disorder
Lee Herring, American Sociological Association
Wade Hitzing, Autism National Committee
Joanne Hewana, *The Blue Sheet*
Perry Hoffman, National Education Alliance for Borderline Personality Disorder
Maia Hurley, Alliance for Children & Families
Larry Icard, University of Pennsylvania
Barbara E. Ines, Institute for the Advancement of Social Work Research
Jocelyn Kaiser, *Science Magazine*
Barbara Keeton, American Psychological Association
Alan Kraut, American Psychological Society
Maury Lieberman, Suicide Prevention Action Network USA, Inc.
Monica Marshall, National Mental Health Association
Carol Mowbray, University of Michigan, Society for Social Work & Research
William Northey, American Association for Marriage & Family Therapy
Dixianne Penney, National Education Alliance for Borderline Personality Disorder
Lucy Perez, National Medical Association
Andrew Pope, Institute of Medicine
Stephanie Reed, American Association for Geriatric Psychiatry
Darrel Regier, American Psychiatric Association
Michelle Rodrigues, SRI, International
Angela Sharpe, Consortium of Social Science Associations (COSSA)
Viviana Simon, Society for Women's Health Research
Mickey J.W. Smith, National Association of Social Workers
Karen Studwell, American Psychological Association
Patricia Watson, National Center for Post-Traumatic Stress Disorder
Larry Werner, Depression Bipolar Support Alliance
Karen White, Children and Adults with Attention-Deficit/Hyperactivity Disorder

NIMH Employees Present

Kathleen Anderson
Bernie Arons
Chiiko Asanuma
Debra Babcock
Karen Babich
Elaine Baldwin
Karen Bartholomew
Alison Bennett
Susan Borja
Beth Bowers
Linda Brady
Susan Brandon
Vanessa Cappell
David Chambers
Lisa Colpe
Bruce Cuthbert
Mark Dzarnolewski
Debra Dabney
Siobhan Deloatch
Jamie Driscoll
David Eskenazi
Wayne Fenton
Rasma Finlayson
William Fitzsimmons
Stephen Foote
Andrew Forsyth
Walter Goldschmidts
Junius Gonzales
Christopher Gordon
Timothy Hays
Michael Hirsch
Michael Huerta
Jane Jacobs
Regina James
Karen Kemp
Kelly Kenneally
Doreen Koretz
Howard Kurtzman
Leticia Lantican
Israel Lederhendler
Jennifer Lewey
David Lozovsky
Ann Maney
Ernest Marquez
Susan Matthews
Annette Mayberry
Donna Mayo
Robert Mays
Steven Moldin
Eve Moscicki
Carmen Moten
Laurie Nadler
Jean Noronha
Grayson Norquist
Kevin O'Brien
Lisa Oken
Jason Olin
Mary Ellen Oliveri
Emeline Otey
Jane Pearson
Willo Pequegnat
Kevin Quinn

Dianne Rausch
Anne Riley
Heather Ringeisen
Judith Rumsey
Agnes Rupp
Michael Sesma
Joel Sherrill
Beth-Anne Sieber
Paul Sirovatka
Melissa Spearing
Ellen Stover
Susan Swedo
Farris Tuma
Benedetto Vitiello
Marilyn Weeks
Gemma Weiblinger
Kate Whelan
Lois Winsky
Clarissa Wittenberg
Steven Zalcman

Other Federal Employees Present

Vicki Levin, Center for Scientific Research, NIH
Anne Mathews-Younes, Center for Mental Health Services
Wendy McLaughlin, NIH

OPEN POLICY SESSION: Call to Order/Opening Remarks

Thomas R. Insel, M.D., Director, NIMH, and Chairman, NAMHC, convened the open policy session of the 203rd Council meeting at 8:30 a.m. on May 9, in Conference Room 10, Building 31C, on the campus of the NIH in Bethesda, Maryland. After welcoming those present, Dr. Insel noted that Dr. Norwood Knight-Richardson would be resigning his Council position and joining the NIMH staff under special arrangements with the University of Oregon Health Sciences Center to help implement the recommendations of The President's New Freedom Commission on Mental Health (see http://www.mentalhealthcommission.gov/) and to advise on biodefense issues.

Dr. Insel extended a special welcome to Ms. Gail Hutchings, Acting Director of the Center for Mental Health Services (CMHS) and Special Assistant to Mr. Charles Curie, Administrator, Substance Abuse and Mental Health Services Administration (SAMHSA). Dr. Insel noted that Mr. Michael English, who previously served as the SAMHSA Liaison Representative to the NAMHC, retired from the Federal Government in April, having served as the Director of the CMHS Division of Knowledge Development and Systems Change.

Future Council Meetings and Approval of the Minutes of the Previous Council Meeting

Before moving to the main agenda, Dr. Insel asked for any comments or corrections to the minutes of the January 17, 2003, Council meeting, and hearing none, Dr. Insel requested and received a motion for approval, which passed unanimously without further discussion.

NIMH DIRECTOR'S REPORT

Dr. Insel noted the historic final sequencing of the human genome. Drs. Insel and Francis Collins have written a commentary that was recently published (see Insel, T.R. and Collins, F.S. "Psychiatry in the Genomics Era." *American Journal of Psychiatry* 160:616-620, 2003) arguing that genomics will ultimately lead to new, targeted therapies for mental disorders. Dr. Insel noted that most of the current psychotherapeutic drugs are variations on those created almost 40 years ago and are limited to targets constituting about .1 percent or even .01 percent of the genome. As at least 55 percent of the genome is expressed in the brain, it is likely that many of the most important new targets for drug development and for therapeutics will derive from as-yet-undiscovered or unnamed genes.

Dr. Insel briefly highlighted the following activities (see the Director's Report, available at www.nimh.nih.gov/council/dirreport_may03.pdf for a more complete description of the meeting activities described below, as well as other activities at NIMH):

Dialogue Four Corners was convened by NIMH in Albuquerque, New Mexico, on April 24, to share information about progress in mental health research and garner input from residents of Arizona, Colorado, New Mexico, and Utah regarding unmet needs and future directions. The primary focus of the meeting was on mental health disparities found in American Indian and Hispanic populations. Similar outreach meetings have been held over the past few years in Alaska, Texas, Chicago, and Pittsburgh (see http://www.nimh.nih.gov/events/townmeetings.cfm for information on these meetings).

Constituency Outreach and Education Program (COEP) partners from each of the States and the District of Columbia gathered in Santa Fe, New Mexico, on April 24-27, to hear presentations by NIMH staff and grantees on mental health topics of current interest. COEP is a nationwide communications initiative of NIMH that enlists State and national organizations in a partnership to help close the gap between mental health research and practice and reduce the stigma of mental illness (see http://www.outreach.nimh.nih.gov/).

Real Men. Real Depression., a public education campaign, was launched at a press conference on April 1 featuring the Surgeon General and other prominent leaders associated with this issue (see http://menanddepression.nimh.nih.gov/). Tom Johnson, former Chairman/CEO of CNN, is helping promote the media effort, which includes TV spots and ads in *The New York Times*, *Forbes Magazine*, and other venues.

The President's New Freedom Commission on Mental Health was established by President Bush through an Executive Order and was charged with conducting a year-long study of the mental health service delivery system, including both the private and public service sectors, with the goal of recommending ways to improve the mental health service delivery system–particularly for adults and children with serious mental illnesses and emotional disturbances. NIMH has collaborated extensively with the Substance Abuse and Mental Health Services Administration (SAMHSA), as well as with representatives from other Federal and State agencies and public sector entities in this review. Although a final report has not yet been issued, the focus likely will be on strengthening a consumer-based and recovery-oriented delivery system and incorporating more evidence-based practices–a recommendation with significance for NIMH's science-to-service research portfolio.

Biodefense activities undertaken as a result of September 11 and the subsequent terrorism alerts have continued at NIH. At Dr. Zerhouni's request, NIH formed a Biodefense Coordinating Committee that is led by the National Institute on Allergy and Infectious Diseases (NIAID) and includes representatives from other Institutes. This Committee is charged with compiling and assembling individual Institute plans and research agendas for a coherent whole for NIH and channeling information regarding biodefense research between and among the Institutes, the NIH director, and relevant external agencies engaged in homeland security. More recently, a Department of Health and Human Services (DHHS)-wide effort under the leadership of U.S. Surgeon General Richard Carmona has been initiated to assess the status of, and to identify gaps in our knowledge base on mental health preparedness for terrorism and our ability to respond to terrorism. A principal goal of the meeting was to plan for a Surgeon General's communication to the American public on mental health preparedness and response. Dr. Insel noted that an NIMH Trauma and Terrorism Consortium has been established under the direction of Dr. Farris Tuma, Chief of NIMH's Traumatic Stress Program. The Consortium will help identify the most effective ways for Federal agencies to communicate with one another and with the public before, during, and after a terrorist attack or other traumatic event; will establish capacity for rapid research; and will review the Institute's research portfolio in this area.

NIH-wide roadmapping exercises, under Dr. Zerhouni's leadership, include a systematic analysis of research opportunities and challenges in an effort to develop a matrix of goals that range in degree of complexity and time required for realization. The roadmaps have led to the development of 15 NIH

workgroups that focus on three areas: (1) finding new pathways for discovery using broad tools such as informatics, chemical genomics, and nanotechnology; (2) building multidisciplinary research teams across Institutes to ensure that the theme of each of the groups is interwoven in the trans-Institute activities designed to meet the goals; and (3) re-engineering the clinical research enterprise through innovative mechanisms such as public/private partnerships and new ways to attract and train the next generation of clinical investigators. NIMH staff members participate on many of the workgroups, which are identifying and prioritizing a matrix of low- and high-risk goals to achieve over a 10-year period.

The NIMH fiscal year (FY) 2003 budget, authorized in February, allocates $1.3 billion to NIMH—an 8.7 percent increase over the FY 2002 budget in both the non-AIDS and AIDS research allocation. The NIMH budget has increased by about 80 percent over the FY 1998 level. The President's FY 2004 budget request for NIMH calls for a 3.1 percent increase over the current funding level.

NIMH's support for research grants is approaching $1 billion this year and includes a dramatic increase in the number of paid grants (i.e., 1,535 paid grants in FY 1987 versus 3,487 paid grants in FY 2002). Along with the greater number of grants are greater costs associated with those grants. A few years ago, the average award for new research project grants was $125,000 per year; the current average award for such grants is $250,000 per year. Since most grants are funded for 4 or 5 years, non-competing continuations represent the largest proportion of funded applications (approximately 70 percent of the total research funding), followed by new applications (approximately 20 percent of the total) and by competing renewal applications (less than 10 percent of the total). The percentage of total awards associated with new grants has remained relatively stable since 2000. Dr. Insel reassured the audience that NIMH will continue to prioritize the funding of R01 grant applications, noting that this is an extraordinary and exciting time for innovative research opportunities that must be anticipated and supported.

To underscore the importance of new scientific discoveries, Dr. Insel referenced the ongoing work of Drs. Mayada Akil, Daniel Weinberger, Joel Kleinman, and others in the Institute's Intramural Research Program (IRP) demonstrating the importance of a functional polymorphism (val^{158}-met) in the catechol-*O*-methyltransferase (COMT) gene (see: "Catechol-*O*-Methyltransferase Genotype and Dopamine Regulation in the Human Brain," available at http://www.jneurosci.org/cgi/content/full/23/6/2008) and "Catechol *O*-Methyltransferase Val^{158}-*Met* Genotype and Individual Variation in the Brain Response to Amphetamine," available at http://www.pnas.org/cgi/content/full/100/10/6186). This extraordinary research suggests that the variation in the COMT gene leads to functional changes in the COMT enzyme, with remarkable consequences for dopamine regulation in the brain and for the brain's response to amphetamine.

Dr. Trey Sunderland's group at the IRP's Geriatric Psychiatry Branch, in collaboration with others, has developed what appears to be the first diagnostic test for Alzheimer's disease (see "Decreased Beta-Amyloid $_{1-42}$ and Increased Tau Levels in Cerebrospinal Fluid of Patients with Alzheimer Disease" available at http://jama.ama-assn.org/cgi/content/full/289/16/2094). The test is based on cerebral spinal fluid (CSF) levels of two key markers: beta-amyloid and tau. The investigators' meta-analysis of previous studies that had been done with CSF measures of these two markers showed that, while neither marker by itself was predictive, the two markers together had considerable power in identifying patients with Alzheimer's disease.

Dr. Insel referenced an extramural study that focused on fragile X syndrome, the most common inherited form of mental retardation in the United States. The study was led by Drs. William Greenough and James Eberwine at the University of Pennsylvania School of Medicine in collaboration with others at the University of Illinois, Urbana-Champaign; the National Institute of Aging; and McGill University (see "RNA Cargoes Associating with FMRP Reveal Deficits in Cellular Functioning in Fmr1 Null Mice." *Neuron* 37:417-431, 2003). The fragile X syndrome is caused by the expansion of the repeated triplet CGG—the first triplet repeat described in modern genetics by Dr. Stephen Warren (now Chairman of the Department of Human Genetics at the School of Medicine at Emory University) some 10 years ago. The Fragile X Mental Retardation-1 (FMR1) gene encodes the FMR protein—one of many proteins that, like a cargo ship, can transport RNA entities from the nucleus to the ribosome—and a protein that is very important for particular classes of RNA. In a technically spectacular study, the researchers developed a technique for identifying the RNA cargoes associated with the FMR protein and found that some of the cargoes are particularly important for dendritic responsiveness and dendritic health. The study offers a model for moving from the molecular to the cellular level in order to understand the dynamics of fragile X that lead to changes in dendritic function and, perhaps ultimately, to mental retardation.

In closing, Dr. Insel reiterated that in this era of the genome, opportunities for progress in neuroscience have never been greater. New tools are available to support breakthroughs in neuroscience that are relevant to mental disorders. However, in this time of tightening budgets, it is more important than ever to set research priorities that closely adhere to NIMH's stated mission—to reduce the burden of mental illness through research on mind, brain, and behavior.

Discussion

Dr. Freedman asked about NIMH's plans for implementing the recommendations of The President's New Freedom Commission on Mental Health. Dr. Insel noted that the final report had not been released yet, but that most of the recommendations likely will pertain to transforming the mental health care delivery system by making it more consumer focused and user-friendly. NIMH's investment in research to provide the evidence base for needed services is critical for informing this process. However, the challenge remains to translate treatments with demonstrated efficacy into the delivery system for patients who need them and to ensure that patients have access to quality care.

Dr. Ritchie, emphasizing that the good mental health of our citizenry is a crucial component of the homeland security response, offered the assistance of the Department of Defense to NIMH in this effort. Dr. Insel observed that, increasingly, experts are recognizing that, in any disaster situation, more individuals are affected by the psychological trauma associated with an event than with direct physical trauma. The Surgeon General has led the way on this issue by speaking openly and passionately about the importance of including a mental health preparedness strategy component in our overall public health preparedness strategy for responding to terrorism.

PSYCHOBIOLOGICAL MECHANISMS OF RESILIENCE AND VULNERABILITY

Dr. Dennis Charney, Chief of the Mood and Anxiety Disorders Research Program and the Experimental Therapeutics and Pathophysiology Branch, IRP, NIMH, spoke about the neurobiology of resiliency to extreme stress and psychopathology.

As background, Dr. Charney referenced prior research studies, mostly examining children, which have found that particular psychological traits, such as optimism, intellectual ability, and emotional intelligence, seem to facilitate resilience. Certain forms of resilience apparently relate to altruism and an active coping style in response to stressors—the ability to convert traumatic helplessness into learned helpfulness/hopefulness. Social supports also are important. Resilience does, in part, depend on environment; only a few people are resilient in almost all environments. Former President Theodore Roosevelt, for example, displayed an extraordinarily broad resilience in dealing with childhood illnesses, combat, and the challenges of the Presidency.

Over the last several years, much has been learned about the components of resilience that might relate to genetics. Scientists are beginning to relate specific genes to specific psychological functions and abilities, neurocircuits, and neurochemicals. Functional polymorphisms have been identified in certain genes (e.g., neuropeptide Y, glucocorticoid receptor, alpha-2-adrenergic receptor, serotonin transporter, BDNF, COMT, MAO-A) that appear to appear to be related to resilience and to a vulnerability to the effects of stress.

NIMH researchers, in collaboration with Dr. Andrew Morgan at Yale University, have been examining the neuroendocrine changes that occur during severe stress and have been trying to determine how these changes relate to performance. The researchers have been studying a likely highly resilient group—members of the U.S. Special Forces who participated in the SERE (Survival, Evasion, Resistance, and Escape) training, which prepares them for working behind enemy lines, being captured, and surviving as prisoners of war (see Morgan CA III, et al. "Plasma Neuropeptide-Y Concentrations in Humans Exposed to Military Survival Training." *Biological Psychiatry* 47(10):902-909, 2000). Participants in the training, mostly men, showed a small increase over baseline in saliva cortisol levels during the capture phase, a massive increase while under interrogation, and a gradual return to baseline levels during recovery. The investigators also found large increases in norepinephrine and increases in neuropeptide Y (NPY). While an increase in norepinephrine enhances the fight/flight reaction and increases alertness, very high levels of norepinephrine produces high levels of fear and anxiety. These reactions seem to be counteracted by simultaneous increases in NPY—an endogenous anxiolytic. Thus, the investigators hypothesized that increased levels of norepinephrine related to an insufficient NPY response will result in vulnerability and poor performance, whereas a robust NPY response will enhance performance. The dehydroepiandrosterone (DHEA) levels of the men in the SERE study also increased under stress. Since DHEA, the most highly concentrated adrenal steroid in the human body, apparently counteracts the effects of cortisol, the investigators hypothesized that a robust DHEA response in relation to increased stress-induced cortisol would be associated with good performance and resilience. Another robust neuroendocrine change that was found was that the levels of testosterone of the men in the SERE training went down during the stress of the capture, which may have negative implications for performance, as testosterone has been related to dominance behavior and assertiveness.

A similar study of participants in a Navy SEAL Survival School was undertaken to ascertain whether neurochemical responses were consistent across different types of stress (see Morgan CA III, et al. Neuropeptide-Y, Cortisol, and Subjective Distress in Humans Exposed to Acute Stress: Replication and Extension of Previous Report." *Biological Psychiatry* 52(2):136-142, 2002). Participants in the SEAL study showed similar stress-related responses to those of the SERE trainees—robust increases in cortisol, norepinephrine, and NPY levels.

The major findings and hypotheses resulting from these studies regarding key neurochemical response patterns to acute stress are:

1. A feedback system that regulates cortisol appropriately seems key to resilience in the face of acute stress. An unconstrained cortisol response that results in hypercortisolemia will result in a vulnerability to depression, hypertension, osteoporosis, and insulin resistance, while an over-constrained cortisol response can lead to hypocortisolemia, which is seen in some patients with post-traumatic stress disorder (PTSD).

2. While a robust DHEA response to stress seems to counteract some effects of high cortisol, a low DHEA response to stress may predispose to psychopathology.

3. The locus coeruleus norepinephrine (LC-NE) plays a key role in activating the sympathetic nervous system and HPA axis, inhibiting parasympathetic outflow and stimulating hypothalamic corticotropin-releasing hormone (CRH). An unrestrained LC-NE system response to stress may lead to psychopathology, including chronic anxiety, hypervigilance, and intrusive memories following traumatic experiences. Some patients with PTSD, panic disorder, or major depression show evidence of persistently heightened LC-NE activity.

4. NPY can modulate the norepinephrine response to stress and is often co-released with norepinephrine. The relationship between norepinephrine function and NPY function may be critical to resilience and vulnerability to stress. The NPY reduces CRH-related actions at the amygdala and reduces the LC firing rate. An adaptive increase in amygdala NPY is associated with a reduced stress-induced anxiety and depression, whereas a low NPY response to stress is associated with increased vulnerability to PTSD and depression.

5. Neurochemical stress-related responses seem to effect performance. Among the SERE trainees, there was a direct correlation between the NPY and the norepinephrine responses, as well as between the NPY and the CORT responses. The higher the NPY response among trainees, the better they performed during interrogation, and the greater the subjective distress reported by SEALS after the navigation experience, the lower their NPY levels.

CRH is another important facet of acute stress response. In numerous preclinical studies, CRH produces behavioral effects that are analogous to human anxiety, fear, and depression. A persistently reduced CRH response seems related to resilience, whereas a persistently increased CRH response predisposes to PTSD, depression, and similar illnesses. Cerebral spinal fluid (CSF) examinations confirm that persons with chronic PTSD have persistently high CRH. Two studies of Vietnam veterans 25 years after their original traumatic combat experience (see Bremner, J.D., et al. "Elevated CSF Corticotropin-Releasing Factor Concentrations in Posttraumatic Stress Disorder."

American Journal of Psychiatry 154(5):624-629, 1997; and Baker, D.G., et al. "Serial CSF Corticotropin-Releasing Hormone Levels and Adrenocortical Activity in Combat Veterans with Posttraumatic Stress Disorder." *American Journal of Psychiatry* 156(4):585-588, 1999) found the veterans' CSF/CRH levels remained elevated.

Since elevated CRH levels may have therapeutic implications, researchers and pharmaceutical companies are developing and testing CRH antagonists. One published proof-of-concept study (see Keck, M.E. and Holsboer, F. "Hyperactivity of CRH Neuronal Circuits as a Target for Therapeutic interventions in Affective Disorders." *Peptides* 22(5):835-844, 2001) showed that higher CRH antagonist doses were as effective as paroxetine in reducing patient-reported symptoms of severe depression over a 30-day period. Other CRH antagonists are being developed for testing on patients with acute stress, chronic depression, and PTSD. The NIMH is conducting toxicology studies as part of a Food and Drug Administration (FDA) approval process for further clinical research on one CRH antagonist, antalarmin.

Other studies provide evidence that patients with chronic PTSD have persistently elevated norepinephrine levels (e.g., Golier J. and Yehuda R. "Neuroendocrine Activity and Memory-Related Impairments in Posttraumatic Stress Disorder." *Developmental Psychopathology* 10(4):857-869, 1998). Patients studied at NIMH with either PTSD or panic disorder have shown exaggerated norepinephrine system responses to the drug yohimbine. Neuroimaging studies confirm that the metabolic response to yohimbine in patients with PTSD is very different than the metabolic response of controls. Since there are functional polymorphisms of the alpha-2 receptor—the receptor upon which yohimbine acts—researchers are studying whether or not the behavioral and cerebral metabolic responses to yohimbine relate to the functioning of the alpha-2 receptor gene.

Additionally, norepinephrine seems to have an important role in encoding traumatic memories. Dr. McGaugh and colleagues (see McGaugh J.L., McIntyre C.K., and Power AE. "Amygdala Modulation of Memory Consolidation: Interaction with Other Brain Systems." *Neurobioogy of Learning and Memory* 78(3):539-552, 2002) have hypothesized that norepinephrine-stimulating beta receptors in the amygdala determine how strongly traumatic memories are encoded. If, as some hypothesize, PTSD and other stress-related disorders reflect indelible memories of the traumatic event, an early intervention that decreases the intensity of the memory encoding activity might be preventative.

Propranolol is being investigated for its potential impact on alerting emotional memories. In an elegant 1994 study, Cahill and McGaugh (see Cahill, L., et al. "Beta-andrenergic Activation and Memory for Emotional Events." *Nature* 371:702-704, 1994) showed that propranolol blocked the enhancing effects of arousal on memory. A number of research groups, including NIMH, are studying whether propranolol administered shortly after exposure to a traumatic event has a preventive effect. A proof-of-concept study (see Pitman R.K., et al. "Pilot Study of Secondary Prevention of Posttraumatic Stress Disorder with Propranolol." *Biological Psychiatry* 51(2):189-92, 2002) showed that in a small sample, propranolol administered to subjects no longer than 6 hours after a traumatic event (subjects were instructed to continue the medication daily for 10 days, followed by a taper period) had positive effects at 3 months on both subjects' PTSD-related symptoms and their physiological responses to scripted imagery of the traumatic event. In a

relevant case study (see Taylor, F. and Cahill, L. "Propranolol for Reemergent Posttraumatic Stress Disorder Following an Event of Retraumatization: A Case Study." *Journal of Traumatic Stress* 15(5):433-437, 2002), propranolol, administered within 48 hours of a trauma to a woman showing symptoms of PTSD and having a history of severe PTSD following previous motor vehicle accidents, had robust effects on reducing the severity of her re-emergent PTSD symptoms.

In summary, Dr. Charney noted, many neurochemical systems respond to acute stress, impacting vulnerability and resilience to psychopathology. These include cortisol, DHEA, CRH, LC-NS, NPY, galanin, dopamine, serotonin, benzodiazepine receptors, testosterone, and estrogen. The overall response pattern to stress, rather than the response of any single system, may be a more useful way to conceptualize resilience and vulnerability. This is consistent with the notion of allostatic load articulated by McEwen and Stellar (see McEwen, B.S. and Stellar E. "Stress and the Individual. Mechanisms Leading to Disease." *Archives of Internal Med*icine 153(18):2093-2101, 1993) that the cumulative impact on health risk from modest dysregulations in multiple systems can be substantial, even if each, individually, has minimal and insignificant health effects.

Several neural mechanisms also are related to resilience and vulnerability to extreme stress and a number of studies, using fMRI and PET imaging to observe brain circuitry, indicate that stress can alter the structure and function of the brain. Dr. Charney presented a slide with the results of 15 studies showing that about 60 percent of patients diagnosed with PTSD had a reduction in hippocampal volume. Similar findings pertain to patients with depression, particularly among those who were traumatized at an early age. A twin study conducted by Gilbertson, M.W., et al. (see "Smaller Hippocampal Volume Predicts Pathologic Vulnerability to Psychological Trauma." *Nature Neuroscience* 5(11):1242-1247, 2002) suggests that a smaller hippocampal volume may be a genetic risk factor for developing PTSD.

These findings have stimulated research studies examining whether the drugs used to treat stress-related disorders, such as PTSD and depression, also effect neuroplasticity and cellular resilience. Studies have found that antidepressants impact the way the hippocampus responds to stress. In animal models, the SSRIs, tianeptine (a novel antidepressant that appears to enhance serotonin uptake) and substance P antagonists have all been shown to reduce stress-induced decreases in hippocampal neurogenesis and to reverse stress-induced decreases in hippocampal volume. Clinical studies are underway to ascertain whether antidepressants also alter the volume of different brain structures in humans.

In conclusion, Dr. Charney summarized, new research is needed to address: (1) the measurable acute post-traumatic diagnostic, psychological, and biological factors that distinguish resilient survivors from vulnerable survivors and also differentiate PTSD-resilient and PTSD-vulnerable survivors; (2) the impact of age, gender, and cultural factors on an individual's response to traumatic stress; and (3) the best methods to evaluate immediate and long-term response to acute stress. This research can be undertaken through epidemiologic studies of the general population and through longitudinal research on specific vulnerable and resilient groups and should be based on models that characterize the full range of acute stress reactions and predict chronicity. He reminded the audience that propranolol and CRH antagonists are promising therapeutics for use in patients experiencing acute stress and that research is needed to test interventions and to prevent potential pathological consequences of traumatic events.

Discussion

Dr. McClelland asked whether an individual's cognitive interpretation of an event might impact the intensity of a stress-induced chemical response, and Dr. Charney responded that the mind-body connection is an important issue and points to the need to collaborate with experts regarding the psychological dimensions that might relate to resilience and vulnerability. This will be the focus of a follow-up study of apparently resilient POWs who recall that trauma as a growth experience with terrible elements that nonetheless influenced them in a positive way.

Dr. Tsuang reported that he is studying twins to examine traits that facilitate resilience (e.g., altruism, optimism, self-confidence, compassion, and forgiveness). A recent paper by his colleagues comparing monozygotic and dizygotic twins showed negative correlations of those traits with neuroticism, anxiety, depression, and substance abuse. Other papers in preparation will extend the work to cholesterol and glucose levels. He reported that about one-third of the variances in these studies appears to be related to genetic differences. This group is now studying PTSD in Vietnam veterans to ascertain how the forgiveness scale relates to veterans' physical and mental health.

Dr. Cameron Ritchie commented on the importance of studying traits that facilitate resilience as POWs are released from military service, go through a decompression phase, and reintegrate home.

To Dr. Lieberman's query about further NIMH investigations of DHEA's effectiveness in modulating GABA and glutamate receptor transmission, Dr. Charney replied that DHEA is a complicated hormone that does seem, for some, to prevent cortisol effects on hippocampal neuronal survivability but, for others, decreases GABA function and may stimulate anxiogenic effects. More studies of DHEA are needed, although it seems to have a positive effect on depression in clinical studies and is being tested on patients with PTSD.

Dr. Wagner asked whether the samples of subjects in the SERE and SEAL studies were sufficiently large to examine the potential impact of adverse early childhood experiences on current neurochemical responses. Dr. Charney said that some of the men in the SERE training had a history of early trauma, although it was not always possible to get accurate details. To the extent that the information was garnered, early trauma did relate to slightly poorer performances.

Dr. Folkman, reporting that her research focuses on psychological stress and coping noted that her findings parallel Dr. Charney's with respect to anabolic and catabolic ratios in the endocrine system and the emotions reported by patients undergoing chronic or acute laboratory stress. Individuals enduring severe and chronic stress report both positive and negative emotions that can be related to a quick or delayed recovery as measured by cortisol response. The concepts of appraisal, threat, and challenge seem to be proximal to an acute stressor and a way of operationalizing such dispositional measures as optimism and a positive coping style. The emotions displayed when a person is actually confronted with an acute stressor seem to balance out—as either more of a threat or a challenge.

Dr. Gunnar remarked that some researchers conceptualize resilience as an individual characteristic while others conclude that it is primarily a product of attachment relationships—especially among children. She encouraged Dr. Charney to focus on both relationships and the neurobiology they may help regulate. Dr. Charney, agreeing that the capacity for attachment is an important variable in how individuals respond to stress, said the NIMH will assess both children's and adults' capacity for attachment behaviors.

Dr. Insel added that newly available data on the long-term consequences of trauma confirm that persons with depression who were traumatized as children respond differentially to psychotherapy than to medication. Those with a history of trauma are particularly responsive to cognitive-behavioral therapy and other forms of psychotherapy rather than medication. Further, it may be important to focus more attention on the neurobiology and genetics of resilience as targets for therapeutics rather than searching for genes causing disease.

THE PARTICIPATION OF WOMEN AND MINORITIES IN RESEARCH

Dr. Ernest Marquez, Director of the NIMH Office for Special Populations (OSP), expanded on the presentation that was begun at the last Council meeting about the representation of women and minority groups in NIH research studies. An NIH policy, mandated by Congress in 1993 as PL 103-43, requires that women and minorities be included in all clinical research studies, including Phase III trials. Grant applications must have an acceptable subject recruitment plan before they can be funded. The need to include specific populations in an application is determined by the topic, condition, or diseases being studied as well as the prevalence of the targeted condition/disease in different populations. Unacceptable recruitment plans are returned to the applicant for revision, and OSP staff reviews the revised plans to determine their acceptability prior to funding.

Displaying the aggregate subject enrollment data for all NIH and NIMH extramural research projects for FY 2000 (available at http://www4.od.nih.gov/orwh/bluerpt.pdf), Dr. Marquez noted that about 61.3 percent of approximately 9.6 million patients enrolled in NIH protocols during FY 2000 were women. About half of the 1.2 million participants in NIMH-sponsored research during FY 2000 were women.

With respect to minority representation, Hispanics accounted for 7.9 percent of all NIH research subjects and 6.2 percent of all NIMH subjects, while Blacks/Non-Hispanics made up 11.3 percent of NIH subjects and 15.4 percent of NIMH subjects. White/Non-Hispanics made up the greatest proportion of NIH research subjects (62.4 percent) and NIMH subjects (65.5 percent). A question that must be asked is whether subject enrollment figures are keeping pace with the demographic changes in this country. This is not the case with Hispanics and does not seem to be the case for American Indians and Alaska Natives who made up only 0.9 percent of NIH subjects and 1.1 percent of NIMH subjects.

The aggregate FY 2000 enrollment data for all NIH Phase III clinical trials show that women account for 70 percent of research subjects; approximately 55 percent of NIMH Phase III trial subjects were female. In terms of specific minority groups, Blacks/Non-Hispanics made up

12.1 percent of NIH Phase III subjects and made up 16.6 percent of NIMH Phase III subjects. Hispanics made up with only 4.1 percent of NIMH research subjects, versus 5.6 percent of NIH subjects.

Although aggregate data help us document that all populations are being included and they provide inclusion trends, aggregate data are not useful for making judgments about the quality of the outcomes. Rather, outcome determinations are made on the basis of each individual application and Initial Review Group/Program review, the topic/condition/diseases being studied, and the prevalence of the condition/disease being studied in different populations.

Among the more than 25,000 research subjects in five DMDBA-sponsored HIV/AIDS behavioral research programs in FY 2002, Blacks made up 28 percent of participants; Hispanics, 23 percent; and American Indians/Native Americans, 12 percent. The large-scale collaborative psychiatric epidemiology surveys conducted by NIMH have varied ethnic/racial group representations, depending on the focus. The National Comorbidity Surveys (replication and adolescent cohorts) indicate that Hispanic/Latinos made up 12 percent of all respondents, as do Blacks/African Americans, but Asian Americans made up only 4 percent of all respondents. In the targeted National Latino and Asian American study (with 5,500 respondents), 48 percent of respondents were Hispanic/Latinos and 48 percent were Asian Americans. For the National Survey of African-Americans (with 7,200 respondents), 57 percent were classified as Black/African American and 26 percent as Black/Caribbean.

DMDBA has made a major budgetary commitment to address the disproportionate impact of HIV infection on ethnic minority populations by increasing efforts to recruit these populations in clinical research studies. Several of the ongoing, large-scale contracted studies that are managed through DSIR appear to be relatively successful in recruiting and retaining women and minorities (see http://www.nimh.nih.gov/studies/index.cfm for a description of these studies). The Sequenced Treatment Alternative to Relieve Depression (STAR-D) study has 17 percent Black/African-American and 8 percent Hispanic/Latino subjects. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study of schizophrenia has 34 percent Black/African-American and 10 percent Hispanic/Latino subjects; while the smaller Treatment for Adolescents with Depression Study (TADS) has 13 percent Black/African-American and 11 percent Hispanic/Latino subjects. The Systematic Treatment for Enhancement Program for Bipolar Disorder (STEP-BD) only includes 4 percent Black/African American subjects and 3 percent Hispanic/Latino subjects. Efforts are underway to increase minority participation in these studies, including the possible addition of study sites that primarily serve minority populations, encouraging the employment of special recruitment coordinators, expanding public awareness of the studies through public service announcements, and translating study materials into languages other than English.

The IRP also is increasing efforts to ensure the inclusion of women and minorities in clinical research. The Research Initiative in Hispanics with Mood Disorders is a model pilot program with Spanish protocols and bilingual nurses, doctors, and social workers (see http://www.nih.gov/news/NIH-Record/06_25_2002/story03.htm). The project, directed by Dr. William Lawson, Howard University, is identifying barriers that inhibit African Americans from participating in clinical research (see http://www.nimh.nih.gov/events/prhoward.cfm).

OSP staff, in partnership with extramural and intramural training staff and staff in other NIH Institutes, are supporting several efforts to increase diversity by promoting a continuum of training opportunities in mental health research—from Ph.D.s to post-doctoral students, to university faculty; by nurturing the development of national mentorship networks; by encouraging new and existing partnerships to enhance science-training goals; by examining and evaluating mechanisms to strengthen minority training and minority institutional infrastructure development; and by providing technical assistance workshops/courses to help develop greater proficiency in writing strong grant applications.

A copy of the NIH Office of Research on Women's Health *Outreach Notebook* that addresses issues of diversity in clinical subject recruitment and retention is available at http://www4.od.nih.gov/orwh/outreach.pdf.

Discussion

Dr. Escobar, acknowledging the improvements in recruiting African Americans into NIMH clinical trials, was concerned that the proportion of Hispanic patients in the NIMH extramural Phase III trials is only 4 percent—despite projections that this group makes up 12 percent of the U.S. population. He said that the mandate is not only to include Hispanic patients, but also to include them in numbers large enough to make reasonable conclusions about their mental health and how they respond to treatment. He reminded the audience that a Council report several years ago highlighted that the small number of minority investigators in mental health fields is a major issue that needed to be addressed see *Racial/Ethnic Diversity in Mental Health Research Careers*, available at http://www.nimh.nih.gov/council/diversity.pdf). Another major disparity that needs attention is the lack of knowledge about mental disorders and their treatments that affect particular minority groups. The major barriers to treatment include language and insurance coverage. Approximately 40 percent of Latinos in the United States are immigrants (most of them are recent arrivals), and about half of them prefer to—or are only able to—speak Spanish. Translated instruments and bilingual/bicultural investigators are extremely important to the provision of adequate treatment, as Dr. Escobar found in his studies conducted in New Jersey.

In responding to Dr. Escobar's comments, Dr. Marquez announced that Dr. Escobar would be joining NIMH on a sabbatical and would be able to assist the Office of Special Populations with diversity issues. He said that it was important to keep in mind former Surgeon General Dr. David Satcher's observation that culture is a critical factor impacting the mental health of minorities as well as the services that they use (see *Mental Health: Culture, Race, and Ethnicity. A Supplement to Mental Health: A Report of the Surgeon General*, available at http://www.surgeongeneral.gov/library/mentalhealth/cre/). Dr. Marquez noted the importance of forming partnerships with relevant organizations such as the National Hispanic Science Network on Drug Abuse and Redes en Acción (Networks in Action), which have networks that can be helpful for mentoring and recruiting purposes, and that he looked forward to the experience and expertise that Dr. Escobar would bring to NIMH.

In response to Dr. Escobar's question about the reasons underlying why more African-Americans participate in clinical trials, as compared with members of other minority groups, Dr. Marquez said that specific efforts, such as the one described at Howard University, are evaluating the importance

of making clinic environments more hospitable to African-American participants. Too few Hispanic and Asian patients find an understanding atmosphere or a familiar culture in research settings. Thus, an effort is underway to find clinicians, researchers, and other staff who know the culture, speak the language, and can make the clinic more inviting.

Dr. Insel commented that recruitment approaches for research studies may not be keeping pace with the country's rapidly changing demographics and that improvements in minority representation likely will take time and continued commitment, as there is no simple answer.

Dr. Tsuang remarked on the small percentage of Asian Americans enrolled in NIMH extramural research studies, noting that Dr. Marquez presented data showing the aggregate enrollment of Asians/Pacific Islanders to be 11.4 percent of all NIH research subjects and 3.8 percent of all NIMH research subjects. In looking at the data, one could ask whether there is a disproportionate selection of Asians/Pacific Islanders, or of any group. The U.S. population demographic percents could be used to weight the percents for the NIH and NIMH data, thus allowing for clearer comparisons of the percents of the groups enrolled.

Dr. Lieberman added that investigators—or NIMH—have an important role in efforts to diversify study populations. While enrollment in the CATIE study accurately reflects the U.S. population demographics for African Americans, Hispanics, and Asians, gender-related recruitment problems, which are characteristics of studies of schizophrenia in general, have plagued this study as well. NIMH has assisted the CATIE study in developing recruitment strategies; it would be useful for NIMH to disseminate information to the wider scientific community on such strategies for intervention research and for disease-associated research.

COLLABORATIVE ACTIVITIES WITH THE SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION (SAMHSA)

Dr. Junius Gonzales, Chief of the Services Research and Clinical Epidemiology Branch (SRCEB), DSIR, spoke of activities in the Bridging Science and Services: An Inter-Agency Initiative that involves collaboration among three NIH Institutes [NIMH, the National Institute on Drug Abuse (NIDA), and the National Institute on Alcohol Abuse and Alcoholism (NIAAA)] and SAMHSA. The Initiative reflects a real commitment to studying a very serious problem—the amount of time needed to move research findings into clinical practice and into policies that facilitate the provision of optimal care. Estimates from the literature indicate that moving findings into practice often exceeds 15 years.

To date, the Initiative has undertaken a number of activities, including: (1) NIH held a briefing for SAMHSA staff in July 2002 that covered the mission of NIMH as it related to the provision of mental health services and research that is undertaken to accomplish that mission; (2) NIMH, NIDA, and NIAAA provided scientific evidence for ten treatments and interventions to their counterpart SAMHSA Center [i.e., the Center for Mental Health Services (CMHS), the Center for Substance Abuse Prevention (CSAP), and the Center for Substance Abuse Treatment (CSAT)] in August 2002; (3) NIMH established a time-sensitive mechanism for fostering realistic research opportunities (see http://grants1.nih.gov/grants/guide/pa-files/PAR-01-136.html) that culminated in a study awarded to a SAMHSA grantee who will evaluate homeless children who are already part

of a grant targeted to homeless families; and (4) NIH convened a technical assistance workshop for 80 SAMHSA grantees in April 2003 to facilitate research collaborations.

In an effort to utilize the "natural laboratories" provided by the sites that participated in the CMHS-funded Comprehensive Community Mental Health Services for Children and Their Families Program initiative, a Program Announcement (PA) was issued (see http://grants1.nih.gov/grants/guide/pa-files/PA-00-135.html) that requested applications for studies of the effectiveness of treatments or services delivered at those sites, the nature and impact of routine clinical practice, and factors related to successful implementation of treatments or services. This PA was accompanied by a jointly conducted NIMH/CMHS technical assistance workshop. Eligibility in this PA will soon be expanded to include Safe Schools/Healthy Students sites. Another small technical assistance workshop is planned for the summer of 2003.

In addition, following up on the concept clearance for a CMHS/NIMH collaboration to award 1 year research planning grants to States to identify factors that facilitate or impede implementation of evidence-based practices (EBPs) (see http://www.nimh.nih.gov/council/cncptgonzales_502.cfm), a Request for Applications (RFA) on the topic was issued in August 2002 (see http://grants1.nih.gov/grants/guide/rfa-files/RFA-MH-03-007.html), following a technical assistance workshop that was held in September 2000 with 60 participants; 37 grant applications were then submitted from mental health and health agencies in 31 States and Puerto Rico. Top-scoring applications covered topics ranging from assertive community treatment, to medication management, to a cognitive-behavioral therapy intervention for depression. These research-planning grants will help States begin building the bridge from science to services by assisting in the formation of new partnerships with academic institutions; by providing a mechanism to identify and address the difficulties encountered by States in moving science findings into practice; and by providing an opportunity to test implementation of EBPs in practice settings and address State level policy issues. The expectation is that successful applicants would then go on to prepare and tailor grant applications for NIH/NIMH research and for SAMHSA service projects.

As next steps for the Science-to-Services Initiative, SAMHSA and its NIMH, NIDA, and NIAAA collaborators have established a process for identifying, prioritizing, and aligning science and services needs. The initial priority was assigned to the homeless mentally ill, with other priorities to follow. NIMH staff members have been working with their counterparts in CMHS to align grant-funding mechanisms. Follow-up activities are planned to develop relationships with new State partners.

Comments by Kevin Hennessy, Ph.D., Senior Health Policy Analyst, Office of the Assistant Secretary for Planning and Evaluation, DHHS

Dr. Hennessy said that the Science-to-Services Initiative has increased the capacities at SAMHSA and NIMH to expand and improve the quality of treatment and prevention research and the quality of services for those in need. He stressed the importance of continued efforts to overcome traditional obstacles to joint funding of priority areas. The ultimate goal of the Initiative, he stressed, must be to decrease the amount of time needed for science-generated knowledge, particularly the knowledge that is generated by randomized controlled trials, to be incorporated into practice. It is unconscionable that an individual who is desperately seeking help for a family member with emerging mental illness can know that proven interventions exist, but that such interventions are not available in ordinary clinical practice.

Comments by Gail Hutchings, M.P.A., Acting Director, CMHS

Ms. Hutchings underscored the important contributions of NIMH to the work of The President's New Freedom Commission on Mental Health, and she noted that she looked forward to the opportunities for CMHS to collaborate with NIMH and other NIH Institutes.

Discussion

Ms. Henry remarked on the importance of rapid dissemination of the findings of the States that will be funded in response to the EBPs RFA as the problems encountered and lessons learned by those States could be very helpful to other States that are likely to implement their own plans for increasing EBPs, with or without Federal funding. Given the States' overwhelming response to the original RFA, Ms. Henry challenged NIMH and SAMHSA to provide funding for a second cohort of EBPs grants. NIMH and SAMHSA, she continued, have major roles to play in implementing the recommendations of the President's Mental Health Commission Report and stimulating wider dissemination and use of EBPs, particularly in public systems, through the funding of additional State grants, would be a wise use of resources.

In response, Dr. Insel noted that the small grants to be awarded to the States are just a beginning. While 20 percent of the States that initially applied for grants in response to the RFA will be funded, 80 percent have needs that must be addressed. Ongoing NIMH/SAMHSA involvement could make a big difference.

Ms. Hutchings commented that financing is another critical issue in the translation of evidence-based practices into services. The 10 EBPs submitted by NIMH to CMHS have been molded into "toolkits" and disseminated to the States. CMHS will examine the financing requirements for those EBPs to determine how payments for some of the services might best be adapted into the State systems of care.

Dr. Gonzales clarified that NIMH and CMHS staff are already working with the States that submitted unsuccessful applications for the EBPs grants to determine whether these applications might be submitted under other funding mechanisms. Planning also is underway for additional follow-up activities.

UPDATES: COUNCIL WORKGROUP ACTIVITIES

Treatment Development Initiative

Dr. Wayne Fenton, Deputy Director of DMDBA, updated Council on the activities of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) contract. While available treatments are relatively effective in treating the positive symptoms associated with schizophrenia, they have little effect on the cognitive deficits of schizophrenia that cause significant disability in patients. Thus, the ultimate goal of the ongoing work is to develop new treatments that target cognition.

The objectives of the contract are to move from basic neuroscience research uncovering some of the mechanisms in the neuropharmacology of cognition to the development of new treatments with novel compounds that are acceptable for human clinical trials. Specific goals are to validate and to publish a standard instrument for measuring cognition in clinical trials; to develop a database of potential lead compounds; and to provide guidelines for collaboration between the Government and the pharmaceutical industry regarding the obtaining of drug registration.

The first phase of the Treatment Development Initiative was the issuance of the MATRICS contract to the University of California, Los Angeles, with Drs. Steven Marder and Michael Green serving as co-principal investigators (details about the MATRICS activities can be found at www.matrics.ucla.edu). The MATRICS project held a conference in April that focused on the neuropsychology of cognitive deficits in schizophrenia to set the stage for developing a standardized instrument. In June, Drs. Carol Tamminga and Mark Geyer will co-chair a conference to look at promising molecular targets for new treatment development. Another conference with industry representatives is scheduled for January 2004 to address substantive issues and intellectual property agreements. A meeting with FDA will be held in April 2004 to provide guidance for industry about next steps.

By September 2003, a RAND panel will be convened to determine what are the elements of cognition that should be assessed with a standardized instrument and what specific measures of those cognitive domains should be included in the instrument. Immediately thereafter, a 12-month psychometric study of the standardized instrument will be initiated to determine the test-retest reliability of the new instrument and its relationship to functional outcome and to establish population norms for the new instrument. During those 12 months, many of the conferences previously mentioned will be held to generate joint FDA/NIMH guidance for industry regarding how to proceed.

NIMH released a Request for Proposals in May to establish a network of treatment development sites—to be known as Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) (see http://www.nimh.nih.gov/grants/SynopNIMH03DM0003.cfm). When a measure is selected and molecular targets have been identified, along with ligands for those targets, a network of three to five clinical trial performance sites will be put into place to move these compounds as rapidly as possible into human clinical trials. One feature of the TURNS network is that, while NIMH plans to support some of the start-up and infrastructure costs that will be built into the

contract, the expectation is that, over time, the network will become increasingly reliant on other sources of funding, including industry-Government collaborations, for moving forward.

Discussion

In response to Dr. Insel's request for more information about the RAND panel, Dr. Fenton explained that the Rand panel will put into place a carefully structured decision-making process that solicits input from a wide variety of stakeholders to arrive at a final consensus on the elements of cognition in schizophrenia that should be assessed and the most appropriate measures of those cognitive domains. While all contributors may not agree with the final decision, the RAND panel ensures agreement that the process leading to the final decision was fair, open, transparent, and based on the best available scientific evidence. Measurement is a critical issue that must be resolved before moving forward in the search for a clinical target. As the FDA cannot accept a single proprietary measure developed by a pharmaceutical company, the FDA has asked NIMH to use its convening authority to establish a battery of measures that is acceptable to a broad range of pharmaceutical companies and academic researchers.

THE NAMHC WORKGROUP ON AGING RESEARCH: AN INTERIM REPORT

Dr. Insel introduced the next speaker, Dr. Charles Reynolds, who chairs the newly created Council Workgroup on Aging Research, which is charged with examining the NIMH research and training portfolio on late-life mood and other mental illnesses. As a Professor of Psychiatry, Neurology, and Neuroscience in the Department of Psychiatry at the University of Pittsburgh School of Medicine and Director of the Mental Health Intervention Research Center for Late-Life Mood Disorders, Dr. Reynolds is an expert in the area of mental disorders and aging.

Dr. Reynolds began his report by thanking NIMH staff and Council members (i.e., Drs. Escobar, Folkman, Knight-Richardson, Squire, and Tsuang) involved in this effort and by reiterating the public health significance of the mental health issues facing the aging population in the United States. The demographics of the United States are changing as the proportion of the aged population continues to increase. The public health burden of mental illness in later life is great and will increase, as documented by the World Health Organization. Further, the high out-of-pocket costs for mental health care for the elderly are a formidable barrier to care for many of them—an issue of great importance impacting the geriatric mental health services research agenda.

The Council Workgroup responds to its charge in an exciting scientific and public health context where many promising areas for research abound, including targeting prevention programs to the elderly; promoting healthy aging; reducing the risk for suicide, especially among the elderly who have the highest suicide rates in this country; addressing disparities faced by elderly minorities in obtaining effective mental health treatment, despite an established evidence base of proven treatments for the elderly; and exploring the promising new leads in aging-related behavioral neuroscience.
The Workgroup has identified two key issues for exploration:

1. What is NIMH's mandate or unique role in aging research? More specifically, is the Institute's investment in mental health and aging research–about 8.5 percent of its research budget–

appropriate to both the current and the projected public health burden of mental illness in old age?

2. Can the current number of Institute-supported research trainees not only sustain but also grow the field of mental health and aging research? While the data show that the total number of entry-level career development awards funded by NIMH over the last 6 years has increased from 32 in FY 1997 and to 87 in FY 2002, the number of entry-level awards over the same period for researchers undertaking careers in aging has remained relatively stable at low levels of five to eight awards per year—an inadequate number to sustain, much less grow, the field of aging research.

Dr. Reynolds noted the investment of the advocacy community in mental health and aging issues and acknowledged the work of the Depression and Bipolar Support Alliance in formulating a consensus statement, to be published in *Archives of General Psychiatry*, and the valuable assistance provided by the National Alliance for the Mentally Ill in formulating a series of research recommendations for NIMH. In addition, the Institute of Medicine's report, "Reducing Suicide: A National Imperative" (see http://www.nap.edu/books/0309083214/html/), represents another important intersection of the research agenda related to suicide, mental health, and aging.

Discussion

Dr. Tsuang commented that collecting normative data for the aging population is a very important task that falls largely within the purview of the National Institute on Aging (NIA) and that it is important for NIMH to partner with NIA to obtain such data. As many NIMH grants now include funding to collect normative data for aging that can be used as a baseline that can be compared with, for example, epidemiological data for Alzheimer's disease, collaboration with NIA might offer an opportunity to maximize research investments across Institutes.

PROGRESS IN AGING AND MENTAL HEALTH RESEARCH

Dr. Richard Hodes, Director, NIA, presented an overview of that Institute's aging portfolio, emphasizing the critical importance of cross-Institute collaboration given that NIA's mission spans many disorders, systems, and organs. He noted that there are many overlaps in research interests with NIMH.

Research programs at NIA fall into four broad categories: behavioral and social research; the biology of aging; the neuroscience of aging (this is the largest program at NIA and has considerable overlap with NIMH in terms of the research on dementia and Alzheimer's disease); and geriatrics and clinical gerontology studies, another area with a significant focus on the intersection between mental health and other medical conditions. In addition to focusing on the many diseases that affect aging (e.g., cardiovascular disease, cancer, and diabetes), particular emphasis is given to examining geriatric syndromes (e.g., falls and frailty) that increase risk among the elderly for disability and loss of independence. Attention also is paid to healthy aging over the lifespan and to identifying various protective factors against age-related disorders—whether physical, psychological, or psychosocial.

Regarding the FY 2002 budget, NIA supported $890 million in aging research compared to $106 million supported by NIMH. That same year, NIA spent $447 million for Alzheimer's disease research, while NIMH invested $70 million in the same area. For mental health, NIMH's total research budget was $1.245 billion compared with the $17 million in mental health research supported by NIA, excluding cognitive research.

The intramural program at NIA, as at other Institutes, is multidisciplinary and offers many opportunities for increasing collaboration with NIMH. This program encompasses 10 scientific laboratories and specialized branches for clinical research.

NIA and NIMH share many research interests, particularly in Alzheimer's disease, where ongoing research is focusing on the genetics of Alzheimer's disease; on neuroimaging, which is critical for assessing changes in cognition; and on the behavioral symptoms and many aspects of caregiving related to Alzheimer's disease and dementia. The two Institutes also share a common research interest in other neurodegenerative diseases associated with aging, such as Parkinson's disease and HIV/AIDS, an area of heightened importance, given the increased incidence of HIV infection and AIDS in the older population. Behavioral genetics and elder abuse are other areas of important overlap of interest. NIA and NIMH are actively collaborating in a variety of activities, including several trans-NIH initiatives involving all or most of the 27 Institutes, such as the Alzheimer's Disease Prevention Initiative, the Healthy Brain Initiative, the Neuroimaging Initiative, and the Genetics Initiative; conferences and workshops; joint RFAs and PAs; and research projects that are co-funded. Joint funding provides the opportunity for staff members of both Institutes to offer their perspectives and wisdom to grantees and maximize the potential value of such studies to the mission of both NIA and NIMH and intramural research efforts.

Dr. Hodes concluded his comments by noting that as is the case at NIMH and at all NIH Institutes, NIA takes very seriously its obligation to translate to the public what it does and the implications of that work and to provide a source of contact for the public. He referred the audience to additional information on aging that is available at the NIA Information Center (phone: 1-800-222-2225); NIA's Alzheimer's Disease Education and Referral Center (phone: 1-800-438-4380 or via the Web at http://www.alzheimers.org/); and the NIA home page at http://www.nih.gov/nia/.

Discussion

When Dr. Reynolds brought up the possibility of NIA's representation on the NAMHC Workgroup on Aging Research, Dr. Hodes welcomed the opportunity and introduced Dr. Marcelle Morrison-Bogorad, Associate Director for NIA's Neuroscience and Neuropsychology of Aging Program, as a likely candidate for participation in that Workgroup.

In response to Dr. Lieberman's question regarding how NIH determines which Institutes should share funding, for example, for Alzheimer's disease research, Dr. Hodes explained that there is a steering committee on Alzheimer's disease with director-level representation from involved Institutes and referral guidelines for grant applications for each Institute. In cases where the most appropriate assignment is not clear, funding decisions often rest upon communications across the Institutes and, at times, on available funding resources. For example, as NIA supports a substantial Alzheimer's centers program, much of the research in this area that involves populations and

biological materials is primarily funded by NIA. As already noted, one way to expand NIMH-NIA collaboration would be for NIMH to utilize NIA's normative data on aging populations to examine areas that are of most proximal concern to NIMH.

When Dr. Lester questioned the extent of NIA's commitment to research training in aging, particularly in the neuroscience of aging, Dr. Hodes remarked that research related to aging is a relatively new discipline that has lagged behind more established disciplines. Training and career development are extremely important issues for NIA that have received progressively more funding, particularly for specific programs, such as a K award targeted at individuals who are clinically trained in areas relevant to dementia and Alzheimer's disease (e.g., psychiatry, neuroscience, and geriatrics). Additionally, NIA is holding discussions with foundations that have active and effective mentoring and career development programs. NIA is about to release new RFAs for career development spanning several clinical areas—including neurology and mental health—that will be jointly supported by NIA and foundations.

Dr. Lieberman, saying he was particularly interested in the NIA study on the longitudinal course of osteoarthritis that combines neuroimaging and clinical characterization, asked whether the FDA had been a participant in identifying targets that might be validated as treatment markers. Dr. Hodes replied that the FDA has been a very enthusiastic participant and that FDA representatives are expressing an openness and willingness to evaluate surrogates that develop and to consider these as legitimate endpoints for clinical studies and interventions. This position has had a positive impact on the pharmaceutical industry, which wants to be certain about a marker and its legitimate role before using it in drug studies.

HIV PREVENTION RESEARCH: ACCOMPLISHMENTS AND CHALLENGES

Dr. Ellen Stover, Director of the Division of Mental Disorders, Behavioral Research and AIDS, introduced the next speaker, Dr. Thomas Coates, as a former Council member who was a major influence in bringing attention at NIMH to the AIDS arena more than 20 years ago, by pointing out the potential devastation caused by the illness. When NIMH launched the AIDS centers program in the mid-1980s, Dr. Coates was the initial co-Principal Investigator on an AIDS center, a first for a behavioral scientist. He subsequently became Director of the University of California at San Francisco (UCSF) AIDS Research Institute and Center for AIDS Prevention Studies, which focuses on behavioral and biomedical aspects of HIV/AIDS. Dr. Stover noted that President Bush recently announced a U.S. commitment of $15 billion to address the international HIV/AIDS epidemic.

Dr. Thomas Coates began his presentation by describing the devastation associated with HIV/AIDS. By the end of 2002, an estimated 42 million people were living with HIV/AIDS, about 30 million of whom resided in sub-Saharan Africa. HIV is one of the most lethal diseases known to humans. Without treatment, 95 to 99 percent of infected individuals die.

The prevention of HIV infection is a simple concept. Unlike airborne infections such as SARS, HIV is relatively difficult to transmit. Although theoretically simple, however, prevention of HIV infection has proven to be relatively difficult. HIV prevention must be approached in various ways to impact risk behavior: at the individual, dyad/family, venue/network, community, and structural (includes laws and policies, the environment, and societal determinants) levels.

At the individual level, Dr. Coates said, most early studies focused on reducing risk among at-risk persons. Project Light was an NIMH-sponsored Phase III clinical trial to reduce HIV-related sexual risk behavior among 3,706 minority group members. Project Light was designed to compare the effectiveness of a cognitive-behavioral intervention to standard care (see NIMH Multisite HIV Prevention Trial Group. "The NIMH Multisite HIV Prevention Trial: Reducing HIV Sexual Risk Behavior." *Science* 19:1889-1894, 1998). The study results document the effectiveness of the approach: participants in the intervention group had fewer unprotected sexual contacts and higher rates of condom use over 12 months compared to the control group, and, for men who used condoms, gonorrhea incidents were reduced by 50 percent. Following this study, a kit containing information on HIV and strategies for reducing risk was prepared for dissemination by the CDC; this kit is being used in a Phase IV dissemination phase of Project Light.

Project EXPLORE is another nearly completed Phase III study supported by NIMH through the HIV Prevention Trials Network that targets men who have sex with men (see http://www.uzucsf.co.zw/research/researchprojects/current/015explore.html). The 4,350 participants in this project were randomized to intensive individual behavioral counseling or HIV voluntary counseling and testing. Outcome data through July 2002 show a 30 percent reduction in HIV acquisition in the experimental group (see Chesney, M.A., et al. *American Journal of Public Health*, in press).

Dr. Coates described "1996" as a watershed year for the HIV/AIDS epidemic. A cover of *Newsweek* read, "The End of AIDS? Not Yet—But New Drugs Offer Hope." Public attention focused on the plight of Magic Johnson, who was living with the AIDS virus but apparently fighting the devastating effects of AIDS with new medications. Experts predicted positive and negative outcomes associated with the increased public attention on HIV/AIDS: On the positive side, anti-HIV drugs would decrease infectiousness and encourage at-risk persons to seek counseling; on the negative side, the potential for living longer with HIV might encourage an increase in risky behavior and infection prevalence as well as drug-resistant HIV infection. Using San Francisco as the case study example, Dr. Coates reported that the first HIV cases were diagnosed in 1981 and prevention efforts started in earnest in 1982-1983. On average, without treatment, people progress from HIV to AIDS in about 10 years. Diagnosis of new AIDS cases peaked around 1982-1983, showing the payoff of prevention efforts. AIDS-related deaths were somewhat delayed, but precipitous decreases in the number of deaths were noted following prevention efforts; and the number of deaths declined more dramatically after the introduction of triple-combination drug therapy. HIV-infected persons are living longer and better, Dr. Coates said. Nonetheless, nearly 9,000 individuals in San Francisco are living with AIDS, and an estimated additional 9,000 individuals are living with HIV, for a total of 18,000 infected individuals. While these persons are living longer, the biggest driver of increased incidence is greater prevalence. As infected persons feel better, the tend to become more sexually active, partly because the disease is not as scary as it once was, and, as a result, San Francisco had about 500 new infections through the mid 1990s and witnessed a resurgence in the number of new cases again, with about 1,100 cases in 2002. San Francisco is not alone in this alarming increase in HIV cases. At the CDC's Tenth Annual Conference on Retroviruses and Opportunistic Infections in 2003, 25 states reported new HIV diagnoses, an increase of 8 percent from 1999 to 2001. Similar data were reported in Vancouver, London, Toronto, Sydney, and in other large cities around in the world.

With the advent of drug therapy, the focus of individual prevention efforts shifted from at-risk individuals to infectious persons. For example, the HIV Voluntary Counseling and Testing (VCT) Study was undertaken in East Africa (Kenya, Tanzania, and Trinidad) between 1993 and 1998. A total of 3,120 individuals were randomized to VCT or health education. An important finding was that HIV-positive individuals were more likely than HIV-negative ones to reduce unprotected intercourse with their primary partner (see The Voluntary HIV-1 Counseling and Testing Efficacy Group. "Efficacy of Voluntary HIV-1 Counseling and Testing in Individuals and Couples in Kenya, Tanzania, and Trinidad: A Randomized Trial. *Lancet* 356(9224):103-112, 2000).

Project REACH in San Francisco is testing three strategies to improve compliance with medication therapy among homeless/marginally housed HIV-positive individuals. To date, there is a high correlation between medication compliance among participants subject to pill counts and those assigned the electronic pill bottle caps. Strikingly, medication non-adherence predicts progression to AIDS and, in turn, mortality. For example, among HIV-infected persons who are medication adherent less than 50 percent of the time, 70 percent have progressed to an AIDS diagnosis by the end of 30 months, compared with HIV-infected participants who adhered to the medication regimen 90 to 100 percent of the time and remained AIDS-free for 30 months after beginning the treatment.

At the level of prevention interventions that focus on dyads/couples, Dr. Susan Allen and colleagues conducted observational studies in Rwanda and Zambia from 1984-1985 that indicated the potential effectiveness of VCT for HIV with couples (see Allen, S., et al. "Confidential HIV Testing and Condom Promotion in Africa. Impact on HIV and Gonorrhea Rates." *Journal of the American Medical Association* 268(23):3338-43, 1992).

At the level of prevention interventions that focus on a network/venue, many studies have focused on the effectiveness of comprehensive sex education delivered in various venues.
Dr. Douglas Kirby, in a summation of research on reducing teen pregnancy (see *Emerging Answers*, May 2001, available at http://www.teenpregnancy.org/resources/data/pdf/emeranswsum.pdf), found the following 10 characteristics of effective sex education programs: have a focus on sexual behaviors; are based on theory; present consistent and clear messages about abstinence and the importance of protection; provide basic and accurate information; address social pressures to have sex; provide examples for practicing communication, negotiation, and refusal skills; teach methods that involve participants; are age-appropriate; last for a sufficient amount of time; and select and train teachers or peer leaders who conduct the sessions. Comprehensive sex education does help delay onset of first intercourse and fosters the use of protection by those who do engage in intercourse.

The Royal Thai Army Study, conducted by Dr. David Celentano during the mid-1990s when HIV was rampant in Thailand, was targeted at army conscripts from the general population entering 8 weeks of basic training. These men were randomized to an experimental squad, a diffusion squad (i.e., in close proximity to the experimental squad but not receiving the intervention directly), or a control squad. The intervention consisted of small group discussions and skills training focused on communications and negotiation. Follow-up assessments over 24-months found that only 3.5 per 1000 of the experimental group acquired HIV compared to 6.8 and 5.5 per 1000 in the diffusion and control groups, respectively. Findings with respect to acquisition of new STDs were more

dramatic: only 4.8 per 1000 of the experimental group were diagnosed compared to 19.6 and 27.5 per 1000 of the diffusion and control groups (see Celentano, DD, et al. "Preventive Intervention to Reduce Sexually Transmitted Infections: A Field Trial in the Royal Thai Army" *Archives of Internal Medicine* 160(4):535-40, 2000).

The C-POL Study, initiated by Dr. Jeffrey Kelly and colleagues, trained popular opinion leaders to diffuse safe sex messages to their peers in environments where susceptible people gather and high-risk sex is negotiated. This intervention was tested in three small southern cities where the gay bar is the main gathering site for homosexual males. Pre/post surveys found important behavior changes among those exposed to the intervention, including decreases in unprotected anal intercourse and reductions in the number of sexual partners (see Kelly, J.A., et al. "Randomised, Controlled, Community-Level HIV-Prevention Intervention for Sexual-Risk Behaviour among Homosexual Men in US cities. Community HIV Prevention Research Collaborative" *Lancet* 350(9090):1500-1505, 1997).

At the level of prevention interventions targeted at community/policy/legal systems, many Government publications from 1991 to 1997 support the effectiveness of needle exchange programs. Specifically, New Haven reported a reduction of 33 percent in HIV incidence, and New York reported a 70 percent reduction. In San Francisco, where five million non-Federally funded needles a year are distributed, the prevalence of HIV infection among injection drug users has fallen from 15 percent to 8 percent. There has been no heterosexual epidemic and no babies born with HIV in San Francisco during the past 10 years.

The MPowerment Program is a system-level intervention that targeted communities of young gay men, aged 18 to 29 years, in three sites. The intervention led to reductions in risk behavior in the experimental community, Albuquerque, while such behavior escalated in the control sites, located in Austin and Phoenix. The project, in a Phase IV effort, is funded by NIMH to disseminate and replicate the approach across the country.

Community-based VCT has been approved for funding but not yet initiated as a large-scale, international project involving the United States, South Africa, Zimbabwe, Tanzania, and Thailand. The plan is to randomize 23 communities in the five nations to receive VCT for HIV and another 23 to receive standard, clinic-based VCT for HIV. This project is designed to change community norms and reduce risk for HIV infection among all community members, whether or not there is direct HIV exposure.

Rapid, same-day testing and diagnosis for HIV have been found effective in sub-Saharan Africa where fewer than 6 percent of a population of 30 million have been tested for HIV given a lack of access to testing. In Zimbabwe, where a mobile van was staffed with outreach workers and counselors, residents in rural areas proved very willing to come for pretest counseling, blood testing, and same-day results. The HIV prevalence for the high-risk young adults tested in Zimbabwe was 30 percent, compared to 17 percent among clients at formal testing centers in Harare.

In conclusion, Dr. Coates posed the question of why, with all the available evidence supporting effective HIV-prevention approaches, does the transmission of HIV continue in this country and

around the world. Science, he said, is still one part of the equation to resolve this human tragedy. A comprehensive HIV-prevention program is an equally important part of the equation and requires a number of ingredients: surveillance, a structured program with clients and providers, capacity building, evaluation, research, and policy/planning.

Switzerland has developed and implemented a comprehensive HIV-prevention program aimed at its young people with good results. By October 1992, about 60 percent of young Swiss adults, aged 17 to 30 years, reported they always used condoms when engaging in sex with casual partners. This was accompanied by a rapid decrease in newly diagnosed HIV infections, particularly among men who have sex with men and injection drug users and, to a slightly lesser extent, among heterosexuals.

Uganda has a comprehensive and effective HIV-prevention program. Between 1989 and 1995, condom use among sexually active men and women in all age groups from 15- to 49-years increased dramatically. This was paralleled by decreases in HIV prevalence among pregnant women between 1990 and 1996.

Thailand also has implemented a comprehensive HIV prevention strategy, resulting in large reductions among urban males in visits to sex workers, decreases in the prevalence of HIV infection among Thai military conscripts, and reductions in the rate of sexually transmitted diseases at government clinics.

Nonetheless, AIDS-related deaths are still increasing rapidly in sub-Saharan Africa compared to the United States, although there is a slight resurgence here. The problem in Africa and other underdeveloped countries is not primarily knowledge, but insufficient resources. Even with the $15 billion pledged by President Bush to fight HIV/AIDS, only 4 million people worldwide will be on antiviral medications by 2007. The available prevention strategies reach too few at-risk persons; too few interventions focus on community and societal levels where they could have the greatest impact.

The U.S. goal is to reduce new HIV infections by one-half. HIV is a completely preventable disease with many available and effective strategies and technologies for ending its scourge. While more research is needed, implementation of what is known would be a major accomplishment.

Discussion

Dr. Insel, after thanking Dr. Coates for a moving presentation, reinforced the importance of diagnosis as part of prevention. He recalled that many patients coming to Grady Hospital in Atlanta already had AIDS and likely had been infected for 8 to 10 years but never realized they had the disease. He wondered how rates of diagnosis in the United States compare with those in Africa and the potential impact of same-day testing and counseling conducted with a mobile van.

Dr. Coates replied that an estimated 65 to 75 percent of individuals with HIV infection in the United States have been diagnosed. However, the 25 to 35 percent who have not been diagnosed are worrisome. They tend to be younger persons, members of minority groups, and women. Rapid, same-day diagnosis has been a tremendous advance. Although available in Africa for 5 years, the FDA did not approve this diagnostic technique for the United States until recently.

To a question from Dr. Freedman about how the presence mental illness affects the behavior of AIDS patients, Dr. Coates replied that, unquestionably, the severe mental illness represented in the homeless and marginally housed populations leads to the spread of HIV. The difficulties encountered in treating these populations also compound transmission potential. Beyond that, individuals with major depression–or even mild depression–tend to engage in more risky behavior. Critical life events (e.g., breakup of relationships) also trigger risky behavior and disinhibition.

With NIMH support, Dr. Coates and colleagues have found a clear association between childhood sexual abuse and later risk behavior among adults. Moreover, gay men report a higher prevalence of childhood sexual abuse than heterosexual men. Men who were abused as children are not only more likely to practice high-risk sexual behavior as adults but also are more likely to have a constellation of associated problems (i.e., depression, substance abuse, difficulties in forming/maintaining intimate relationships, and HIV infection). This cluster of mental health-related issues may actually be fueling a new wave of the HIV epidemic in this country, especially among men who have sex with men.

Dr. Escobar, noting Dr. Coates' interest in Latin America and his emphasis on international collaboration, asked what he had learned in foreign countries that could be applied to work in the United States and might undergird the importance of increasing international research collaborations in other areas. Dr. Coates responded that the first gratifying lesson learned through working in foreign countries is that people are more alike than not, and among the major commonalities are concerns with health, family, and friends. Also, the stigma associated with HIV has been a huge impediment to progress in preventing HIV. The recent RFA on stigma funded by the NIMH and other institutes (see http://grants1.nih.gov/grants/guide/rfa-files/RFA-TW-03-001.htm) should lead to an increased understanding of the universality of stigma in different cultures. A third lesson is that outside of Denmark, Sweden, the Netherlands, most of the world does not like to talk about sex, although people like to engage in it. The wide discrepancy between an official code of conduct and the practiced code takes on different structures in different societies. Fourthly, HIV is shaking up societies in unimaginable ways. More specifically, the HIV epidemic in most of Spanish-speaking Latin America is almost entirely among men who have sex with men. Similarly, legal changes in sub-Saharan Africa are beginning to improve the status of women who, by virtue of their previous economic and social positions and also because of their biology, have

been most vulnerable to HIV, even as adolescents. These changes have trans-national applications. Finally, the HIV epidemic has forced researchers to consider cross-cultural adaptations of psychological, social, and theoretical approaches. Some successful approaches in the United States can be taken abroad, but indigenous approaches learned in South Africa and Uganda can also be brought back here.

When Dr. Lester asked for more specific estimates of the cost to turn around the epidemic in sub-Saharan Africa, Dr. Coates replied that, at minimum, it would probably take $10 billion a year to scale-up prevention, build capacity, and purchase sufficient anti-viral drugs.

After complimenting Dr. Coates on his powerful presentation, Dr. Essock pointed out another area of synergy between the AIDS portfolio and other NIMH research—by successfully engaging communities in research efforts and rolling out projects in politically sensitive environments, the information gleaned by AIDS investigators could translate to other centers in forming community partnerships and conducting mainstream research in local settings. It is no coincidence that successful prevention interventions and services researchers have been funded by the NIMH AIDS program. In that sense, methods dissemination, Dr. Essock said, offers a great opportunity for research advancements in other areas of science.

CONCEPT CLEARANCES

Dr. Insel introduced the concept presentations (see http://www.nimh.nih.gov/council/conceptindex.cfm) and noted that the concepts to be described are likely to become research initiatives provided that adequate funding is available to support them.

Intervention Research in Anorexia Nervosa

Dr. Joel Sherrill, Chief of the Psychosocial Treatment Research Program, Division of Services and Intervention Research (DSIR), noted that the proposed RFA for anorexia interventions was motivated by the lack of research on this debilitating eating disorder. The proposed RFA would solicit grant applications for clinical research on psychosocial and/or pharmacological interventions, including larger-scale randomized clinical trials to provide more definitive tests of existing interventions and explore mediators and moderators of outcomes. Studies also are needed on more effective relapse and prevention procedures, target populations and age groups, and effective delivery systems and settings as well as rigorous tests of inpatient maintenance and booster therapies. Studies of adolescents that test developmentally informed interventions and explore the inclusion of parents might be especially profitable as would prevention interventions that target youth with recognized risks (e.g., elevated weight and body image concerns). More attention also needs to be given to specialized interventions for ethnic minority groups and for males.

Developing Centers on the Prevention of Suicide

Dr. Jane Pearson, Associate Director for Preventive Interventions, DSIR, and head of the NIMH Suicide Consortium, explained that the 2002 IOM report, "Reducing Suicide: A National Imperative", which was produced in collaboration with the National Institute on Drug Abuse, the

National Institute on Alcohol Abuse and Alcoholism, CDC, and the Substance Abuse and Mental Health Services Administration, as well as NIMH and several Council members, offers the primary justification for the proposed center mechanism. Although the body of evidence on risk factors is growing, more knowledge is needed about protective factors. While the number of trials focused specifically on reducing suicidality is increasing, no center has been established to promote networks among the handful of established investigators in this field, to foster careers of new investigators with an interest in the topic, or to advance scientific methods for evaluating suicide prevention efforts and disseminating findings.

Sharing Research Resources for Genetic Studies on Autism

Dr. Steven Moldin, Associate Director, Division of Neuroscience and Basic Behavioral Science (DNBBS), explained the background for this proposed supplement to existing research resources. Autism is a disabling childhood disorder and a significant public health burden with a complicated etiology. While the identification of genes for autism could revolutionize diagnosis, treatment, and prevention efforts, the search has been hampered by the relative rarity of the disorder and the need for large compilations of family pedigree data. This initiative proposes to assemble and pool all of the separate datasets from small autism pedigree studies funded by NIH, thereby increasing the statistical power to identify autism genes, stimulating and accelerating the sharing of available data, and facilitating future molecular genetic studies. Two large sets of autism data are already available to the scientific community–or will be shortly. The first, funded by NIMH's Autism Genetics Initiative, includes samples collected at Stanford University through a collaborative project conducted by Drs. Joseph Piven and Susan Folstein, and the Autism Genetics Research Exchange–an effort initiated by Cure Autism Now (CAN), a patient support and advocacy group. The National Alliance for Autism Research (NAAR) also is sharing pedigrees in the worldwide Autism Genome Project that has just begun. Currently, the NIMH initiative has collected 350 pedigrees, and the CAN effort has contributed another 400 samples, yielding 750 pedigrees in the general scientific domain within the next 18 months.

The proposed initiative would add an additional 400 pedigrees, funded primarily via administrative supplements to existing NIH genetics research projects that collect autism pedigrees. The money would fund re-consenting the subjects, redrawing of blood, and standardizing phenotyping to facilitate data pooling. The initiative also would support the evaluation of programs from which applications are received as well as the assembly and distribution of the DNA, clinical data, and data analyses to the scientific community through the NIMH Center for Collaborative Genetic Studies.

The Pharmacogenomics of Mood and Anxiety Disorders

Dr. Steven Moldin summarized the value of this proposed RFA as contributing to the discovery of novel drug targets for new therapeutic compounds and, ultimately, helping genomic medicine individualize drug response profiles for patients that will revolutionize clinical psychiatry. The initiative would fund projects that study the genome of patients with mood and anxiety disorders to ascertain the genetic basis of their therapeutic responses to anxiolytic, antidepressant, antipsychotic, and antimanic drugs. Apparently, side effects to therapeutic compounds reflect individual variations in the genome known as single nucleotide polymorphisms (SNPs)–the most common

type of genetic variation in the genome. It is possible to compare large samples of patients who do and do not experience deleterious side effects and then develop a therapeutic response profile that would be useful for ascertaining, by DNA examination, whether someone is at increased risk for a side effect. This approach could be very helpful in predicting, for example, which patients with schizophrenia are likely to develop agranulocytosis after taking the antipsychotic medication, clozapine. Ultimately, the initiative can also facilitate the identification of new clinical targets. Essentially, the initiative is expected to stimulate SNP mapping and facilitate the construction of SNP profiles for therapeutic responses or adverse events that would change how drugs are prescribed as well as identify new targets for drug discovery. Widespread sharing of the genetic profiling information generated by the initiative with the scientific community is a key component of this effort. The proposed RFA would support five to seven R01 or R21 projects that use high through-put genotyping and state-of-the art bioinformatics to profile SNPs.

Developing Translational Research on Mechanisms of Extinction Learning

Dr. Kathleen Anderson, Chief of the Cognitive Neuroscience Program, DNBBS, recalled Dr. Insel's presentation at the previous Council meeting on animal research studies that implicate the prefrontal cortex in extinguishing previously learned fear responses and data from patients with post-traumatic stress disorder showing prefrontal activity deficits in response to emotional stimuli. These findings suggest opportunities for translational research focused on understanding how deficits in extinction learning are related to psychiatric anxiety disorders characterized by maladaptive fear responses.

Research on the behavioral and neural mechanisms underlying extinction learning and consolidation lags behind studies of fear conditioning. Anxiety and related fear disorders are increasingly prevalent–estimated to affect over 19 million persons in the United States alone. Translational research on extinction learning is needed to enhance an understanding–and stimulate development–of novel pharmacological, behavioral, and cognitive therapies for psychiatric disorders characterized by the inability to extinguish maladaptive fear responses or consolidate safety signals. Dr. Anderson noted that NIMH is sponsoring a workshop this summer on the mechanisms of extinction learning that will bring together basic and clinical scientists with expertise in this area. An exploratory development R21 mechanism is anticipated that will foster collaborative networks among basic and clinical researchers, pilot studies to demonstrate the feasibility of particular translational research approaches, and the development of basic research methodologies with clinical applications.

Non-Invasive, Near-Infrared Optical Neuroimaging

Dr. Michael Huerta, Associate Director of Scientific Technology and Research, DNBBS, described a proposed RFA to develop optical technologies for non-invasive neuroimaging of the functioning human brain. The premise is that imaging neural activity is crucial to the brain and behavioral research in humans. Current neuroimaging technologies have many limitations, including an inability to combine spatial and temporal resolution. A modality is needed that can simultaneously provide millisecond temporal resolution and millimeter spatial resolution of brain activity. Because optical technologies are diverse, sophisticated and robust, they offer many options for development. A non-invasive, near infrared optical imaging technology would facilitate important studies of

functional cortex connectivity and organization and help advance knowledge of brain behavior in health and illness. Such a technology would also facilitate brain studies among children who would not be frightened by the methodology. The proposed RFA would solicit R01 and R21 applications to develop technologies that use non-invasive, near infrared light for imaging neural activity in milliseconds and millimeters. Grants in this area would also increase an understanding of the basis for the biological signals being examined. Responsive applications would include engineering of the photon source/detector configurations for detecting signals in specific brain regions or whole-head imaging as well as development of algorithms for reconstructing data in three dimensions and formulation of data analysis approaches and tools.

Development of Parallel Measures in Bipolar Disorder Research

Dr. Debra Babcock, M.D., Medical Officer, Clinical Neuroscience Research Branch, DNBBS, summarized the rationale for this proposed initiative as a critical shortage of research addressing etiology in bipolar disease that has been cited by numerous workgroups, including the Mood Disorder Strategic Workgroup convened by Dr. Steven Hyman. Studies in response to the proposed initiative might address cycling of mood or other phenomena that seem to parallel mood swings (e.g., changes in appetite, sleep habits, menstrual cycles, and seasonal affects). The development of objective tools that can be used in both animals and humans also is encouraged as are translational approaches focusing on one or more relevant aspects of bipolar illness that can be modeled in both animals and humans and possibly serve as an endophenotype for bipolar disorder (e.g., specific cognitive processes, fluctuations in mood states or irritability, sleep or circadian rhythms, or psychomotor activity levels). Other potential areas of interest include animal models of neuroimaging or postmortem characteristics and pharmacological or pharmacogenetic indices.

PUBLIC COMMENT

Dr. Darrel Regier, American Psychiatric Association (APA), opened the public comment period with several announcements. The APA membership is concerned, he said, that monies are being redirected away from the mental health service system into other types of services (i.e., criminal justice, disability, child welfare, or emergency medical care) at a time of severe funding shortages. Secondly, the APA is looking forward to the IOM report on research training because of its deep concern about the paucity of research investigators within the academic psychiatric community. Relatedly, the APA appointed Council member Dr. Charles Reynolds as a new member of the Residency Review Committee for Psychiatry and hopes he will call attention to the research training needs of psychiatrists as this field develops. Further, APA anticipates a productive collaboration with NIMH, NIDA, NIAAA, and international colleagues at WHO and elsewhere to identify a research basis for changing the DSM criteria for mental disorders. Also, APA's academic consortium has participated in advocacy efforts to solicit a larger share of research appropriations for NIMH, NIDA, and NIAAA. The professional community is very concerned about this issue.

The next speaker, Dr. Lucy Perez, immediate past President of the National Medical Association (NMA) and representing the current President, Dr. Natalie Carroll, requested that NIMH and Council members continue collaborating with and supporting the NMA's scientific assembly that will meet the first week of August in Philadelphia. The NMA looks forward to working closely with Council on issues related to HIV disease, engaging physicians in research, and identifying new

populations to investigate as well as recruiting new scientists. The NMA would specifically like to collaborate in recruiting under-represented minorities to participate in pharmacogenomic research.

Ms. Cynthia Folcarelli, representing the National Mental Health Association (NMHA), expressed her enthusiasm for the initiatives presented at this meeting. Increasing the enrollment of people of color and women in clinical trials is very important as is work with older adults. The NMHA is excited about the upcoming eating disorders initiative and research on understudied aspects of resilience as well as vulnerability. However, the Association hopes that more attention will be given to the behavioral and environmental underpinnings of resilience and vulnerability to psychiatric disorders/stress as well as the biochemical foundations. Ms. Folcarelli thanked NIMH for working closely with the Center for Mental Health Services, SAMHSA, on the science to practice initiatives. Finally, she reminded those in attendance that May is Mental Health Month when relevant materials are distributed nationwide and local NMHA groups participate in mental health-related activities.

Adjournment

There being no further comments, Dr. Insel adjourned the 203rd meeting of the NAMHC at 1:40 p.m. on May 9, 2003.

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

_____

Thomas R. Insel, M.D., Chairperson